

EXHIBIT F



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ANTIEPILEPTIC DRUGS AND SUICIDALITY

Drug Class: Antiepileptic drugs

Drug Names (NDA Numbers): Carbamazepine (21-710)
Divalproex (18-723, 19-680, 21-168)
Felbamate (20-189)
Gabapentin (20-235, 20-882, 21-129, 21-216)
Lamotrigine (20-241, 20-764)
Levetiracetam (21-035, 21-505, 21-872)
Oxcarbazepine (21-014, 21-285)
Pregabalin (21-446)
Tiagabine (20-646)
Topiramate (20-505, 20-844)
Zonisamide (20-789)

Indication(s): Epilepsy, psychiatric disorders, other

Date: 23 May 2008

Biometrics Division: Division of Biometrics 6

Statistical Reviewer: Mark Levenson, Ph.D.

Statistical Team Leader: C. George Rochester, Ph.D., RAC

Medical Division: Division of Neurology Products

Clinical Team: Evelyn Mentari, MD
Alice Hughes, MD
John Feeney III, MD
Marc Stone, MD

Project Manager: Jacqueline Ware, Pharm.D., RAC

Keywords: Epilepsy, psychiatric, bipolar, suicide, suicidality, meta-analysis

TABLE OF CONTENTS

List of Tables	3
List of Figures	4
Executive Summary	5
1.1 Overview	5
1.2 Findings.....	5
1.3 Conclusions	6
2 Introduction.....	7
2.1 Background	7
2.2 Review Objectives	7
3 Data Sources	7
3.1 Data Requests.....	7
3.2 Trial Summary	9
4 Methods.....	12
4.1 Endpoints	12
4.2 Analysis Population	13
4.3 Subgroups and Special Populations	13
4.4 Statistical Methods.....	14
5 Patient Summary	16
5.1 Drugs and Demographics.....	16
5.2 Discontinuation and Duration	20
6 Findings.....	22
6.1 Suicidal Behavior or Ideation	22
6.2 Suicidal Behavior and Suicidal Ideation.....	26
6.3 Sensitivity Analysis	27
6.4 Exploratory Analysis	32
7 Findings in Special/Subgroup Populations	35
7.1 Drug Groups.....	35
7.2 Trial Indication.....	37
7.3 Demographics	39
8 Post-Hoc Analyses	45
8.1 Lamotrigine Additional Data	45
8.2 Alternative Age Subgroups.....	47
9 Summary and Conclusions	47
9.1 Review Summary.....	47
9.2 Conclusions.....	49
10 References.....	49

LIST OF TABLES

Table 1: Suicidality Events and Codes.	8
Table 2: Antiepileptic Drugs under Review.	9
Table 3: Indication Categories.	10
Table 4: Trials by Comparator Type and Drug.	11
Table 5: Trials by Indication Group and Therapy (Monotherapy, Adjunctive Therapy, Other).	12
Table 6: Patients by Treatment Arm and Comparator Type.	16
Table 7: Patients by Treatment Arm and Drug, Placebo-Controlled Trials.	17
Table 8: Patients by Indication Group and Drug, Placebo-Controlled Trials.	18
Table 9: Demographics by Treatment Arm, Placebo-Controlled Trials.	19
Table 10: Patients by Drug Class and Treatment Arm, Placebo-Controlled Trials.	20
Table 11: Patient Treatment Discontinuation and Duration by Treatment Arm, Placebo-Controlled Trials.	21
Table 12: Events by Type and Treatment Arm, Placebo-Controlled Trials.	22
Table 13: Suicidal Behavior or Ideation Events and Patients by Drug, Placebo-Controlled Trials.	23
Table 14: Suicidal Behavior or Ideation Hazard Estimates by Treatment Arm, Placebo-Controlled Trials.	32
Table 15: Events from Patients with Multiple Events, Placebo-Controlled Trials.	34
Table 16: Placebo and Drug Suicidal Behavior or Ideation Event Rates and Risk Difference by Indication, Placebo-Controlled Trials.	38

LIST OF FIGURES

Figure 1: Mean Trial Duration by Treatment Arm, Placebo-Controlled Trials.....	21
Figure 2: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled Trials.	25
Figure 3: Suicidal Behavior versus Suicidal Ideation Odds Ratio Estimates, Placebo- Controlled Trials.	26
Figure 4: Suicidal Behavior or Ideation Risk Difference Estimates, Placebo-Controlled Trials.	28
Figure 5: Suicidal Behavior or Ideation Rate Ratio Estimates, Placebo-Controlled Trials.	31
Figure 6: Kaplan-Meier Suicidal Behavior or Ideation Incidence Curves by Treatment Arm, Placebo-Controlled Trials.	33
Figure 7: Suicidal Behavior or Ideation Odds Ratio Estimates by Drug Group, Placebo- Controlled Trials.	36
Figure 8: Suicidal Behavior or Ideation Odds Ratio Estimates by Indication Group, Placebo-Controlled Trials.	37
Figure 9: Suicidal Behavior or Ideation Odds Ratio Estimates by Age Group, Placebo- Controlled Trials.	40
Figure 10: Suicidal Behavior or Ideation Odds Ratio Estimates by Gender, Placebo- Controlled Trials.	41
Figure 11: Suicidal Behavior or Ideation Odds Ratio Estimates by Race Group, Placebo- Controlled Trials.	42
Figure 12: Suicidal Behavior or Ideation Odds Ratio Estimates by Setting, Placebo- Controlled Trials.	43
Figure 13: Suicidal Behavior or Ideation Odds Ratio Estimates by Location, Placebo- Controlled Trials.	44
Figure 14: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled and Low-Dose-Controlled Trials.....	45
Figure 15: Suicidal Behavior or Ideation Odds Ratio Estimates with Additional Lamotrigine Data, Placebo-Controlled Trials.....	46
Figure 16: Suicidal Behavior or Ideation Odds Ratio Estimates by Post-Hoc Age Group, Placebo-Controlled Trials.	47

EXECUTIVE SUMMARY¹

1.1 Overview

The Food and Drug Administration (FDA) concerned about the potential for elevated risk of suicidality (suicidal behavior or ideation) from the use of antiepileptic drugs carried out a meta-analysis of 11 drugs. Antiepileptic drugs are also used for indications other than epilepsy including psychiatric disorders.

In March 2005, FDA sent letters to sponsors of antiepileptic drugs requesting that they submit data from placebo-controlled trials for the FDA to review the possible association of suicidality events and antiepileptic drugs. Letters in July 2005, May 2006, and January 2007 requested additional information to obtain the data necessary for the review. The letters specified detailed instructions for the identification of suicidality events and the format of the data to be submitted.

Prior to the analysis of the data, medical reviewers in the Division of Neurology and statistical reviewers in the Quantitative Safety and Pharmacoeconomics Group agreed upon the definition of the research objectives, endpoints, study population, and subgroups and upon the specification of the statistical methods. These elements were incorporated into a statistical analysis plan prior to the review. The statistical methods maintained the integrity of placebo-controlled trials. This allowed for trials to have different background rates of events.

1.2 Findings

There were 199 placebo-controlled trials consisting of 27,863 patients in drug arms and 16,029 patients in placebo arms from 11 drugs that formed the primary analysis population.

The average age of patients was 42 years. The majority of patients were female (55%), white (79%), and from North American locations (61%). The placebo patients had statistically higher treatment duration (77 days for placebo versus 73 days for drug). There were no statistical differences among the baseline characteristics of the drug and placebo patients for age, gender, race, and location.

There were 4 completed suicides among drug patients and none among placebo patients. The majority of suicidality events for both drug and placebo patients were Suicidal Ideation. The second most frequent type of event was Suicide Attempt. Without adjusting for differences among trials, 0.37% of the drug patients had a Suicidal Behavior or Ideation event versus 0.24% of the placebo patients.

¹ This review replaces the March 5, 2008 version. Two small discrepancies in the data have been corrected for this version.

Overall, patients who received an antiepileptic drug had statistically significant increased risk of Suicidal Behavior or Ideation relative to placebo patients. The estimated overall odds ratio (OR) of a drug patient experiencing a Suicidal Behavior or Ideation event versus a placebo patient was 1.80 (95% CI: 1.24, 2.66). The results for individual drugs were generally consistent with the overall result. Suicidal Behavior had a larger estimated odds ratio [2.92 (95% CI: 1.44, 6.47)] than Suicidal Ideation [1.45 (95% CI: 0.93, 2.30)]. Sensitivity analyses showed that the results were robust to statistical methods and differences in the treatment durations between the treatment groups.

Indication and location appeared to have the largest effects on the odds ratio among the subgroups considered. The epilepsy indication subgroup had the largest estimated odds ratio [3.53 (95% CI: 1.28, 12.10)] compared to the psychiatric indication subgroup [1.51 (95% CI: 0.95, 2.45)] and the other indication subgroup [1.87 (95% CI: 0.81, 4.76)]. However, the psychiatric indication subgroup had the largest placebo risk and the risk difference for the psychiatric indications subgroup was the largest. The estimated odds ratio for the Non-North American subgroup [4.53 (95% CI: 1.86, 13.18)] was notably larger than that of the North American subgroup [1.38 (95% CI: 0.90, 2.13)].

The higher risk of events for the drug-treated patients was observed as early as 1 week from initiating treatment until at least 24 weeks. After 24 weeks, it was not possible to draw conclusions due to the scarcity of data beyond 24 weeks.

There was no obvious pattern in the drug effect with respect to age subgroups. Likewise, there were no patterns with respect to subgroups based on gender, race, setting, and prespecified drug groups (sodium channel blocking, GABAergic and GABA-mimetic, and carbonic anhydrase inhibitors).

1.3 Conclusions

In conclusion, antiepileptic drugs are associated with increased risk of suicidality relative to placebo in randomized placebo-controlled trials. The effect appears consistent among the group of 11 drugs. There are 1.9 per 1000 (95% CI: 0.6, 3.9) more antiepileptic drug patients than placebo patients who experience Suicidal Behavior or Ideation. In terms of adjusted risk estimates for the treatment groups, 0.43% of the drug patients experience Suicidal Behavior or Ideation compared to 0.24% of the placebo patients.

There is no obvious subgroup of patients to which the increased risk is specifically attributed. The increased risk was seen in almost all subgroups, although epileptic and Non-North American patients may have higher relative risks.

2 INTRODUCTION

2.1 Background

The Food and Drug Administration (FDA) concerned about the potential for elevated risk of suicidality (suicidal behavior or ideation) from the use of antiepileptic drugs carried out a meta-analysis of 11 drugs. Antiepileptic drugs are also used for indications other than epilepsy including psychiatric disorders. In March 2005 FDA initiated requests to the sponsors of antiepileptic drugs for data to address the suicidality concern.

Prior to the analysis of the antiepileptic data, medical reviewers in the Division of Neurology and statistical reviewers in the Quantitative Safety and Pharmacoepidemiology Group agreed upon the definition of the research objectives, endpoints, study population, and subgroups and upon the specification of the statistical methods. These elements were incorporated into a statistical analysis plan prior to the review.

This review replaces the March 5, 2008 version. Two small discrepancies in the data have been corrected for this version.

2.2 Review Objectives

1. Examine whether 11 antiepileptic drugs as a group are associated with increased risk of suicidality relative to placebo in randomized placebo-controlled trials.
2. Examine whether the risk of suicidality varies by (a) individual drug, (b) drug subgroups, (c) indication subgroups, and (d) demographic subgroups.

3 DATA SOURCES

3.1 Data Requests

In March 2005, FDA sent letters to sponsors of antiepileptic drugs requesting that they submit data from placebo-controlled trials for the FDA to review the possible association of suicidality events and antiepileptic drugs. Sponsors of all drugs with available registration trials were contacted. Letters in July 2005, May 2006, and January 2007 requested additional information to obtain the data necessary for the review. The letters specified detailed instructions for the identification of suicidality events and the format of the data to be submitted.

3.1.1 Trial Inclusion Criteria

The final directions to the sponsors called for the submission of data for all randomized parallel-arm, placebo-controlled trials, regardless of indication and duration, with at least 30 patients total. Trials may have had active-control arms as well. In addition to parallel-arm trials, data from the first period of cross-over trials that otherwise met the trial inclusion criteria were also included. In addition to placebo-controlled trials, trials with subtherapeutic comparator arms, known as "low-dose placebo" were to be included. The low-dose controlled studies were not included in the primary analysis. The July 2005

FDA letter specified that studies with ongoing blinded treatment phases should not be included.

3.1.2 Identification of Suicidality Events

FDA specified the procedure for the identification of suicidality events. The procedure called for a search of “possibly suicide-related” adverse events (PSRAEs). The search was to be strictly limited to events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. All deaths and serious adverse events (SAEs) were to be included as PSRAEs. In addition, events were identified through a search of specified text-strings in the adverse event data. For each PSRAE, a narrative was to be prepared.

Based on blinded versions of the narratives, the PSRAEs were to be classified into mutually exclusive suicidality events using the approach employed in classification of outcomes as implemented in the pediatric antidepressant analysis (Posner et al. 2007). Table 1 gives the suicidality events. Sponsors were responsible for the classification of events.

Table 1: Suicidality Events and Codes.

Event Code	Event
0	No Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Not enough information, non-fatal

3.1.3 Dataset Definition

FDA specified the format of patient-level and trial-level datasets to be submitted. The patient-level dataset was to have one record per event. Patients with multiple events were to have multiple records in the dataset corresponding to each event. Patients without events were to be assigned an event code of 0. The patient-level dataset included variables for trial identification, patient identification, age, gender, race, setting of trial (inpatient, outpatient, both), location of trial (North America, Non-North America), treatment drug, event code, day of event, and discontinuation status. For location, FDA did not specify the meaning of North America.

The trial-level dataset summarized and characterized the trial. This information included indication, nominal duration, treatment arm sizes, inclusion and exclusion criteria, dosage, and design features.

3.2 Trial Summary

Sponsors submitted datasets from 12 drug programs. One of these drugs, vigabatrin, is not currently approved in the United States and was not part of the review. Table 2 gives the names of the 11 drugs that were included in the review.

Table 2: Antiepileptic Drugs under Review.

Drug	NDA Number
Carbamazepine	21-710
Divalproex	18-723, 19-680, 21-168
Felbamate	20-189
Gabapentin	20-235, 20-882, 21-129, 21-216
Lamotrigine	20-241, 20-764
Levetiracetam	21-035, 21-505, 21-872
Oxcarbazepine	21-014, 21-285
Pregabalin	21-446
Tiagabine	20-646
Topiramate	20-505, 20-844
Zonisamide	20-789

The medical officer, Dr. Evelyn Mentari, Division of Neurology Products, performed some initial data processing of the submitted patient-level datasets including:

1. Checking the correctness of the data submission to the FDA instructions
2. Concatenating the data from the 11 drug programs into a single dataset
3. Removing trials based on exclusion criteria (described below)
4. Reducing multiple events in a single day to a single event (described below)
5. Removing patients under the age of 5
6. Creating indication categories (described below)

Trials were excluded if the duration was less than 7 days, there were fewer than 20 patients in any arm, all patients were less than 5-years old, or the trial had a randomized withdrawal design (including withdrawal to placebo).

For patients with multiple events on a single day, only the most critical event (based on the event codes shown in Table 1) on the day was retained.

The medical officer categorized the numerous indications into 21 indication categories. These 21 indication categories were further categorized into three categories: (1) epilepsy, (2) psychiatric, and (3) other. Table 3 gives the 21 indication categories and their further classification into three categories.

Table 3: Indication Categories.

Epilepsy	Psychiatric	Other
Epilepsy	Anxiety	Agitation
	Binge eating disorder	Chronic pain
	Bipolar disorder	Fibromyalgia
	Depression	Impaired cognition
	Panic disorder	Insomnia
	Post-Traumatic Stress Disorder	Migraine
	Schizophrenia	Neuropathy
	Social phobia	Obesity
		Radiculopathy
		Spasticity
		Tremor

Note: The other indication category included volunteer studies.

The review was based on the datasets prepared by Dr. Mentari and provided on 7 November 2007.

Table 4 gives the number of trials by comparator type and drug. There were 210 trials. Of these, 199 were placebo controlled and 11 were low-dose controlled. No study had both a placebo arm and a low-dose arm. There were 23 trials that also had an active-control arm.

Table 4: Trials by Comparator Type and Drug.

Drug	Number of Trials		Total
	Placebo-Controlled	Low-Dose Controlled	
Carbamazepine	3	0	3
Divalproex	13	1	14
Felbamate	6	3	9
Gabapentin	28	0	28
Lamotrigine	27	2	29
Levetiracetam	21	0	21
Oxcarbazepine	10	1	11
Pregabalin	38	1	39
Tiagabine	6	0	6
Topiramate	42	3	45
Zonisamide	5	0	5
Total	199	11	210

Table 5 gives the number of trials by indication group and therapy (monotherapy, adjunctive therapy, and other). In the majority of epilepsy trials (81%), the drug was used in combination with other therapies as adjunctive therapy. In contrast, in the majority of psychiatric trials (86%), the drug was used as monotherapy.

Table 5: Trials by Indication Group and Therapy (Monotherapy, Adjunctive Therapy, Other).

Therapy	Indication Group			Total N=210 n (%)
	Epilepsy N=73 n (%)	Psychiatric N=56 n (%)	Other N=81 n (%)	
Monotherapy	14 (19)	48 (86)	61 (75)	123 (59)
Adjunctive Therapy	59 (81)	8 (14)	12 (15)	79 (38)
Other	0 (0)	0 (0)	8 (10)	8 (4)

Note: Other therapy includes trials with optional adjunctive therapy and a trial in which one patient cohort received adjunctive therapy and one patient cohort did not receive adjunctive therapy.

4 METHODS

The statistical analysis plan (SAP) including the definitions of the endpoints, study population, subgroups, and statistical methods were prespecified prior to conducting the review. As stated above, these definitions and specifications were chosen by medical reviewers in the Division of Neurology and statistical reviewers in the Quantitative Safety and Pharmacoepidemiology Group. Deviations from and additions to the SAP are noted.

4.1 Endpoints

4.1.1 Primary Endpoint

The primary endpoint was *Suicidal Behavior or Ideation*. A patient had this endpoint if the patient had any of the following suicidality events:

- Completed suicide
- Suicide attempt
- Preparatory acts toward imminent suicidal behavior
- Suicidal ideation

4.1.2 Secondary Endpoint

There were two secondary endpoints. A patient had the endpoint *Suicidal Behavior* if the patient had any of the following suicidality events:

- Completed suicide
- Suicide attempt

- Preparatory acts toward imminent suicidal behavior

A patient had the endpoint *Suicidal Ideation* if the patient had only a Suicidal Ideation event. Note that the endpoint *Suicidal Ideation* was not part of the SAP.

4.2 Analysis Population

The primary analysis population was all patients in test drug and placebo arms from placebo-controlled trials that met the trial and patient inclusion criteria described in Section 3.2.

4.3 Subgroups and Special Populations

4.3.1 Drugs

Each drug was considered separately

4.3.2 Drug Groups

Three groups of drugs were considered. These groupings were chosen by the medical officers from the Division of Neurology. Each group of drugs was compared to the complementary group of drugs. Note that the drug groups are not mutually exclusive or exhaustive.

1. Sodium Channel Blocking Drugs

- Carbamazepine
- Lamotrigine
- Oxcarbazepine
- Topiramate
- Zonisamide

2. GABAergic Drugs and GABA-mimetic Drugs

- Divalproex
- Gabapentin
- Pregabalin
- Tiagabine
- Topiramate

3. Carbonic Anhydrase Inhibitors

- Topiramate
- Zonisamide

4.3.3 Trial Indication

Three indication groups were considered as defined in Table 3:

1. Epilepsy
2. Psychiatric Indications
3. Other Indications

4.3.4 Demographics

The following subgroup classes were considered:

1. Age
 - 5-17

- 18-24
- 25-30
- 31-64
- ≥ 65
- 2. Gender
 - Male
 - Female
- 3. Race
 - White Caucasian
 - Other
- 4. Setting
 - Inpatient or Inpatient/Outpatient Combined
 - Outpatient
- 5. Location
 - North America
 - Non-North America

The age subgroups were chosen to be the same as used in FDA analysis of the antidepressant suicidality. Only two race subgroups were used because the overwhelming majority of patients were white. "Other" for race included African American, Hispanic, Asian, and other. For location, FDA did not specify the meaning of North America.

4.3.5 Comparator Type

The group of patients from low-dose-controlled trials was considered. This group was compared to the primary analysis group of placebo-control trial patients and the group of patients from both placebo-controlled and low-dose-controlled trials. For the analysis of patients from both types of trials, the test drug patients were compared to the patients in the corresponding trial control arm patients (placebo or low-dose).

4.4 Statistical Methods

4.4.1 Primary Method

The primary analysis method was the exact method for a stratified odds ratio and associated 95% confidence interval (Cytel 2005, Ch. 19). The odds ratio was in terms of patient units. The stratification factor was the trial.

4.4.2 Sensitivity Methods

Three sensitivity analyses were employed to examine the robustness of the primary method.

4.4.2.1 Zero-Event Trials

The first sensitivity analysis examined the consequences of the fact that a large number of the trials were expected to have no events. The exact method for a stratified odds ratio does not make use of these trials. The Mantel-Haenszel risk difference and associated confidence interval (Greenland and Robins 1985), which makes use of these trials, was

used for this sensitivity analysis. However, if there are no events for any trials, for example in a subgroup, then the estimated variance will be zero. In this case, it is not appropriate to use the variance estimate, and no estimate and confidence intervals were presented.

4.4.2.2 Trial Heterogeneity

The second sensitivity analysis examined between-trial heterogeneity of the effect measure. Zelen's test (Cytel 2005, Ch. 19), an exact test, was used to test the hypothesis of a common odds ratio. However, because of the small number of events, it was expected that there would be little power to detect heterogeneity of the odds ratio across trials. The result of the test was intended for qualitative purposes.

The trial weight of the Mantel-Haenszel odds ratio estimator was used to quantitatively identify trials with large influence. The weight was equal to $(\text{control patients with events}) * (\text{test patients without events}) / (\text{total patients})$. Trials with no events had a weight of zero. For trials with events in one arm only, the weight was equal to $(\text{control patients with events} + 0.5) * (\text{test patients without events} + 0.5) / (\text{total patients} + 2)$. Note that the SAP incorrectly specified "+1" rather than "+2" in the denominator.

A generalized linear mixed model (GLMM) (McCulloch and Searle 2001) was used to estimate the overall odds ratio in the presence of trial heterogeneity of the odds ratio. The model used the binomial error distribution and logit link function. The model included fixed effects for the trial and treatment effects and a random effect on the trial-level for the treatment-trial interaction. The estimate and the 95% confidence interval of the treatment effect were qualitatively compared to those from the primary method to examine the effect of trial heterogeneity. The confidence interval of the variance component of the random effect was also examined to evaluate trial heterogeneity.

4.4.2.3 Duration Differences

The third sensitivity method, which was not part of the SAP, examined the consequences of the observed difference in treatment duration between the treatment arms. The method was similar to the primary method, but used person-time rather than patients as the unit of analysis (Cytel 2005, Ch. 15). Because the duration difference was small, an assumption of constant hazards was not key.

4.4.3 Exploratory Methods

4.4.3.1 Time Pattern

Kaplan-Meier incidence curves were used to examine the time-pattern (hazard function) of the *Suicidal Behavior or Ideation* events. For patients with multiple events, only the most critical event was used. No stratification was employed in the analysis.

4.4.3.2 Demographics, Duration and Discontinuation

Differences in treatment arms within trials of demographics, treatment duration, and premature discontinuation of patients were examined. For categorical variables, p-values for differences between treatment groups were based on the Cochran-Mantel-Haenszel test stratifying on trial. For continuous variables, p-values and least-squares means were based on a 2-way ANOVA controlling for trial.

4.4.3.3 Multiple Events

For each patient that had multiple events, the events were summarized.

4.4.4 Missing values

There were no missing values allowed for trial, treatment arm, and event codes. Therefore, the primary analysis was not be affected by missing values. For each subgroup analysis, all patients with the necessary information to determine the subgroup membership were used.

4.4.5 Statistical Significance

Statistical significance refers to a two-sided type 1 error of 0.05. Because the analysis was exploratory in nature, no adjustments for multiplicity were be made.

5 PATIENT SUMMARY

5.1 Drugs and Demographics

Table 6 gives the number of patients by treatment arm and comparator type (placebo-controlled versus low-dose-controlled). Overall, there were 43,892 patients in the placebo and the drug arms from placebo-controlled trials. There were more patients in the drug arms (27,863) than in the placebo arms (16,029) for these trials. There were 1,587 patients from low-dose-controlled trials. Not included in the table were an additional 1,997 patients from active-control arms among the placebo-controlled and low-dose-controlled trials.

Table 6: Patients by Treatment Arm and Comparator Type.

Comparator Type	Treatment Arm			Total
	Drug	Placebo	Low-Dose Placebo	
Placebo-Controlled	27863	16029	0	43892
Low-Dose Controlled	788	0	799	1587
Total	28651	16029	799	45479

Table 7 gives the number of patients by treatment arm and drug for placebo-controlled trials. The drugs topiramate and pregabalin accounted for approximately half of the overall patients: 27% for topiramate and 24% for pregabalin.

Table 7: Patients by Treatment Arm and Drug, Placebo-Controlled Trials.

Drug	Treatment Group		
	Drug N = 27863 n (%)	Placebo N = 16029 n (%)	Total N = 43892 n (%)
Carbamazepine	252 (1)	250 (2)	502 (1)
Divalproex	1327 (5)	992 (6)	2319 (5)
Felbamate	170 (1)	170 (1)	340 (1)
Gabapentin	2903 (10)	2029 (13)	4932 (11)
Lamotrigine	2865 (10)	2070 (13)	4935 (11)
Levetiracetam	2554 (9)	1549 (10)	4103 (9)
Oxcarbazepine	1342 (5)	827 (5)	2169 (5)
Pregabalin	7201 (26)	3125 (19)	10326 (24)
Tiagabine	835 (3)	608 (4)	1443 (3)
Topiramate	7742 (28)	3971 (25)	11713 (27)
Zonisamide	672 (2)	438 (3)	1110 (3)

Table 8 gives the number of patients by indication group and drug. Seven of the 11 drugs had patients in all three indication groups. Large percentages of gabapentin and topiramate patients were in the Other Indication group (non-epilepsy, non-psychiatric). Overall, the Other Indication group had the most patients with 48% of the patients. The Epilepsy and Psychiatric Indication groups had similar percentages of the patients to each other with roughly 25% of the patients each.

Table 8: Patients by Indication Group and Drug, Placebo-Controlled Trials.

Drug	Indication Group			Total N
	Epilepsy n (n/N%)	Psychiatric n (n/N%)	Other n (n/N%)	
Carbamazepine	0 (0)	502 (100)	0 (0)	502
Divalproex	147 (6)	1285 (55)	887 (38)	2319
Felbamate	340 (100)	0 (0)	0 (0)	340
Gabapentin	1485 (30)	331 (7)	3116 (63)	4932
Lamotrigine	1408 (29)	2313 (47)	1214 (25)	4935
Levetiracetam	1634 (40)	1609 (39)	860 (21)	4103
Oxcarbazepine	1110 (51)	115 (5)	944 (44)	2169
Pregabalin	1685 (16)	3204 (31)	5437 (53)	10326
Tiagabine	939 (65)	504 (35)	0 (0)	1443
Topiramate	1346 (11)	1933 (17)	8434 (72)	11713
Zonisamide	848 (76)	0 (0)	262 (24)	1110
Total	10942 (25)	11796 (27)	21154 (48)	43892

Table 9 gives the demographics of the patients by treatment arm. For age, gender, race, and location there were no statistically significant differences between the treatment arms. P-value for setting could not be calculated due to the sparseness of the data, but the observed percentages were similar between the treatment arms.

The least-squares means for age was 42 for both treatment arms. The least-squares means control for differences among the trials and are more appropriate measures than the ordinary means in the context of the meta-analysis, which controls for differences among the trials. Roughly 5% of the patients were under the age of 18 and 13% of the patients were age 65 or older. A majority of the patients were female (55%). A large majority of the patients were white Caucasian (79%). A large majority of patients had out-patient treatment only (92%) and a majority of the patients were in North America (61%).

Table 9: Demographics by Treatment Arm, Placebo-Controlled Trials.

Characteristic		Drug N=27863	Placebo N=16029	Total N=43892	P-Value
Age (Years)	5-17	1292 (5)	1119 (7)	2411 (5)	0.2745
	18-24	2126 (8)	1296 (8)	3422 (8)	
	25-30	2633 (9)	1568 (10)	4201 (10)	
	31-64	18157 (65)	9990 (62)	28147 (64)	
	≥ 65	3653 (13)	2056 (13)	5709 (13)	
	Missing	2 (0)	0 (0)	2 (0)	
	Mean (Std.)	45 (17)	43 (18)	44 (17)	0.2184
	Least-Squares Mean	42	42		
	Range (Min – Max)	(5 -100)	(5 – 99)	(5 – 100)	
Gender	Female	15586 (56)	8686 (54)	24272 (55)	0.6557
	Male	12276 (44)	7343 (46)	19619 (45)	
	Missing	1 (0)	0 (0)	1 (0)	
Race	White Caucasian	22302 (80)	12541 (78)	34843 (79)	0.1703
	Other	3588 (13)	2264 (14)	5852 (13)	
	Missing	1973 (7)	1224 (8)	3197 (7)	
Setting	Inpatient or Both	1893 (7)	1411 (9)	3304 (8)	NA
	Outpatient	25970 (93)	14618 (91)	40588 (92)	
	Missing	0 (0)	0 (0)	0 (0)	
Location	North America	16841 (60)	9941 (62)	26782 (61)	0.9523
	Non-North America	11022 (40)	6088 (38)	17110 (39)	
	Missing	0 (0)	0 (0)	0 (0)	

Notes: Results for categorical variables are expressed as counts and percentages of treatment arm. P-values for categorical variables are based on Cochran-Mantel-Haenszel test controlling for trial. P-values and least-squares means for continuous variables are based on 2-way ANOVA controlling for trial. P-value for setting could not be calculated due to the sparseness of the data.

Table 10 gives the number of patients for the three drug groups. No p-values are available because drug class does not vary within a trial. As stated in Section 4.3, the three drug groups are not mutually exclusive. Drugs and therefore patients appear in multiple drug groups.

Table 10: Patients by Drug Class and Treatment Arm, Placebo-Controlled Trials.

Drug Group		Drug N=27863	Placebo N=16029	Total N=43892
Sodium Channel Blocking	Yes	12873 (46)	7556 (47)	20429 (47)
	No	14990 (54)	8473 (53)	23463 (53)
GABAergic and GABAmimetic	Yes	20008 (72)	10725 (67)	30733 (70)
	No	7855 (28)	5304 (33)	13159 (30)
Carbonic Anhydrase Inhibitors	Yes	8414 (30)	4409 (28)	12823 (29)
	No	19449 (70)	11620 (72)	31069 (71)

5.2 Discontinuation and Duration

Table 11 gives the treatment discontinuation status and the duration by treatment arm. A statistically significant larger percentage of drug patients discontinued prematurely than placebo patients. The placebo patients had a statistically significant larger least-squares mean for duration than drug patients. However, the drug patients had a larger ordinary mean for duration than the placebo patients.

The difference in results between the least-squares means and the ordinary means is influenced by a single trial. Figure 1 plots for each trial, the mean placebo duration versus the mean drug duration. The overall consistency of the durations within trials is seen by the fact that most trials fall near the 45-degree line. The trial with the largest durations (topiramate OBES002) had a large imbalance of patients between the arms: 960 drug patients and 322 placebo patients. This imbalance in arm sizes had large influence on the ordinary means. Removing this trial, the ordinary means were more similar, 82 days for each arm. Overall, for 131 of the 199 trials, the placebo arm had a higher duration than the drug arm.

Since the meta-analysis controlled for differences in trials, the least-squares means are more appropriate to examine differences in duration. The least-squares means show that the placebo patients had larger durations (77 days for placebo versus 73 days for drug). If events were related to duration, the placebo patients may be expected to have more events independent of any treatment effect. The person-time analysis described in Section 4.4, which was not part of the Statistical Analysis Plan, was performed to account for the possibility of a duration effect.

Table 11: Patient Treatment Discontinuation and Duration by Treatment Arm, Placebo-Controlled Trials.

Characteristic		Drug N=27863	Placebo N=16029	Total N=43892	P-Value
Discontinue	No	17889 (64)	11118 (69)	29007 (66)	<.0001
	Yes	9974 (36)	4911 (31)	14885 (34)	
	Missing	0 (0)	0 (0)	0 (0)	
Duration (Days)	Mean (Std.)	90 (89)	87 (78)	89 (85)	<.0001
	Least-Squares Mean	73	77		
	Range (Min – Max)	(0 – 575)	(1 – 582)	(0 – 582)	
	Missing	9	8	17	

Notes: Results for categorical variables are expressed as counts and percentages of treatment arm. P-values for categorical variables are based on Cochran-Mantel-Haenszel test controlling for trial. P-values and least-squares means for continuous variables are based on 2-way ANOVA controlling for trial.

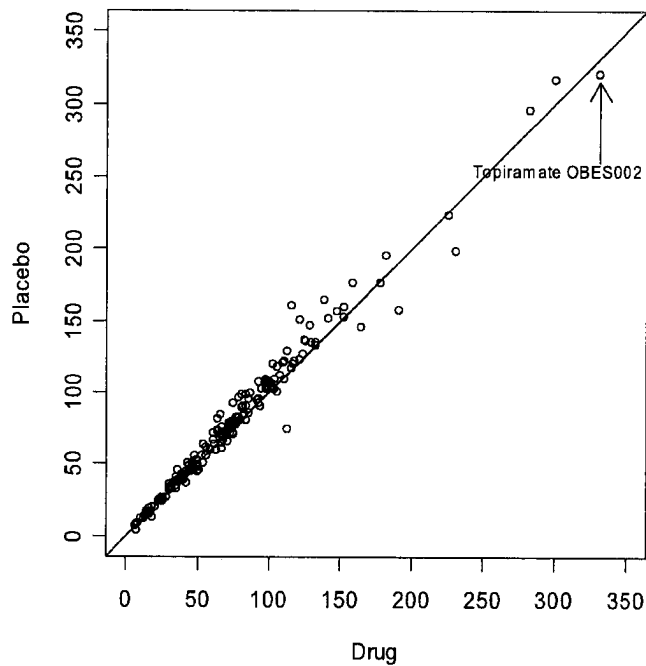


Figure 1: Mean Trial Duration by Treatment Arm, Placebo-Controlled Trials.

6 FINDINGS

6.1 Suicidal Behavior or Ideation

Table 12 gives the number of patients with a Suicidal Behavior or Ideation event by type of event and treatment arm. There were 4 completed suicides among patients in the drug arms and none among patients in the placebo arms. Of the 4 completed suicides, 2 were in the Epilepsy Indication subgroup and 2 were in the Psychiatric Indication subgroup. The majority of events for both arms were Suicidal ideation. The second most frequent type of event for both arms was Suicide Attempt. Note that as seen on Table 6, there were more drug patients than placebo patients. Without adjusting for differences among trials, 0.37% of the drug patients had a Suicidal Behavior or Ideation event versus 0.24% of the placebo patients. Of the 199 placebo-controlled trials, 66 (33%) had at least one Suicidal Behavior or Ideation event in the test drug or placebo arms.

Table 12: Events by Type and Treatment Arm, Placebo-Controlled Trials.

Event	Drug	Placebo	Total
Completed suicide	4	0	4
Suicide attempt	30	8	38
Preparatory acts	3	1	4
Suicidal ideation	67	29	96
Total	104	38	142

Notes: Events include only the most critical event for each patient.

Table 13 gives the number of patients with a Suicidal Behavior or Ideation event, the number of patients, and the crude odds ratios by drug. The drug felbamate had no events and therefore the odds ratio for the drug is not defined. The drug tiagabine had events only in the drug arm and therefore the odds ratios for this drug was infinity. No drug had events only in the placebo arm. The range of the finite crude odds ratios was from 0.66 to 2.57.

Table 13: Suicidal Behavior or Ideation Events and Patients by Drug, Placebo-Controlled Trials.

Drug	Drug Events/Patients	Placebo Events/Patients	Crude OR
Carbamazepine	2/252	3/250	0.66
Divalproex	11/1327	9/992	0.91
Felbamate	0/170	0/170	ND
Gabapentin	2/2903	1/2029	1.40
Lamotrigine	27/2865	11/2070	1.78
Levetiracetam	8/2554	2/1549	2.43
Oxcarbazepine	2/1342	1/827	1.23
Pregabalin	7/7201	2/3125	1.52
Tiagabine	2/835	0/608	Inf.
Topiramate	40/7742	8/3971	2.57
Zonisamide	3/672	1/438	1.96
Total	104/27863	38/16029	1.58

Notes: Events include only most critical event for each patient.
ND: Not defined. Inf.: Infinity.

Figure 2 gives a forest plot of the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by drug and overall. The estimated overall odds ratio was 1.80 (95% CI: 1.24, 2.66). The odds ratio was greater than 1 and the confidence interval did not contain the value of 1. Therefore, the drugs were associated with statistically significant increased risk of Suicidal Behavior or Ideation events relative to placebo.

Based on the overall odds ratio estimate and the observed rate of 0.24% for Suicidal Behavior or Ideation events among placebo patients, there was an estimated 1.9 per 1000 (95% CI: 0.6, 3.9) more antiepileptic drug patients than placebo patients who experienced Suicidal Behavior or Ideation in placebo-controlled trials. In terms of adjusted risk estimates for the treatment groups, 0.43% of the drug patients experienced Suicidal Behavior or Ideation compared to the 0.24% of placebo patients.

Among the 10 drugs with any events, the estimated odds ratios for 8 drugs were greater than 1. For 2 of these 8 drugs, the confidence interval did not contain the value of 1.

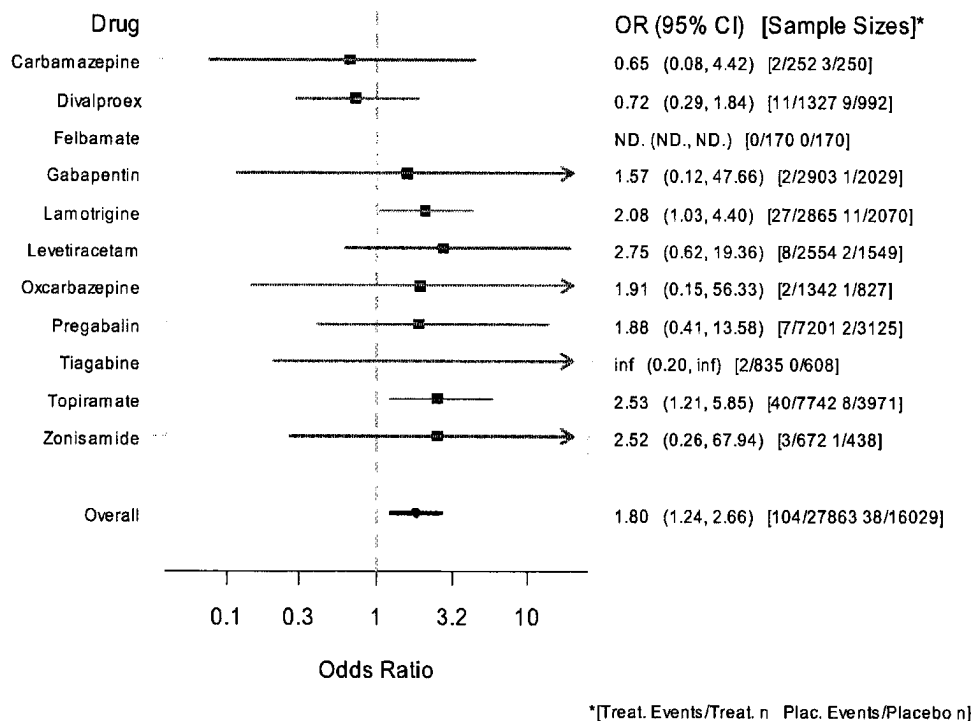


Figure 2: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled Trials.

6.2 Suicidal Behavior and Suicidal Ideation

Figure 3 gives the overall odds ratio estimates for the two endpoints: (1) Suicidal Behavior and (2) Suicidal Ideation. The odds ratio estimate for Suicidal Behavior was greater than the odds ratio for Suicidal Ideation. The confidence interval for Suicidal Behavior did not contain the value of 1, whereas the confidence interval for Suicidal Ideation contained the value of 1.

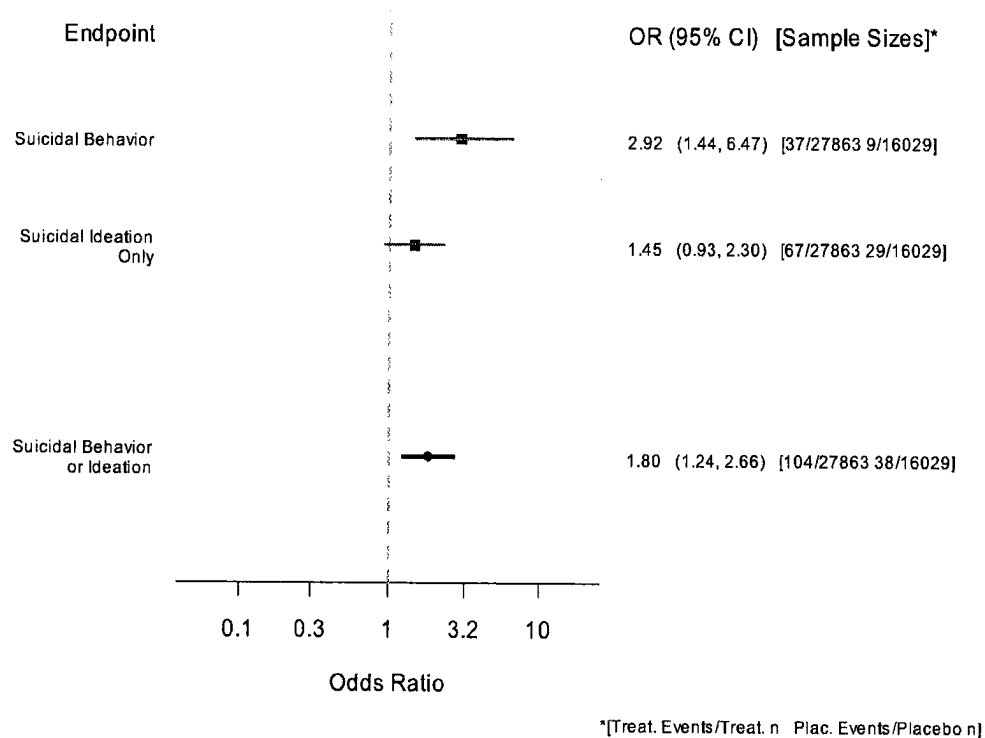


Figure 3: Suicidal Behavior versus Suicidal Ideation Odds Ratio Estimates, Placebo-Controlled Trials.

6.3 Sensitivity Analysis

6.3.1 Zero-Event Trials

Figure 4 gives the estimated risk differences and 95% confidence intervals for Suicidal Behavior or Ideation by drug and overall. Unlike the odds ratio analysis, this risk difference analysis makes use of trials without any events.

The overall risk difference was 1.79 (95% CI: 0.70, 2.87) per 1000 patients. The risk difference was greater than 0 and the confidence interval did not contain the value of 0. As was the case, for the odds ratio analysis, this result supports the finding that the drugs were associated with statistically significant increased risk of Suicidal Behavior or Ideation events relative to placebo. For each of the 11 drugs, the risk difference estimate had the same direction as the odds ratio estimate relative to the null value of no effect.

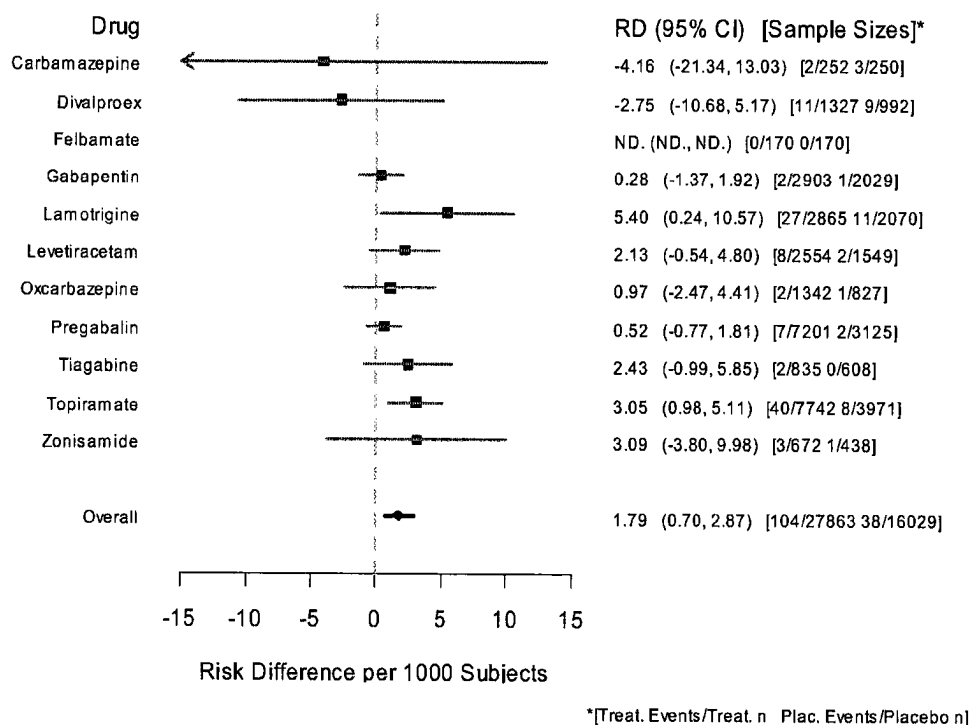


Figure 4: Suicidal Behavior or Ideation Risk Difference Estimates, Placebo-Controlled Trials.

6.3.2 Trial Heterogeneity

The primary analysis method was a fixed-effect method. Fixed effect methods assume that all the trials had a common treatment effect. The p-value based on Zelen's test for the null hypothesis that all trials had a common odds ratio test was 0.735. This value does not provide evidence for trial heterogeneity in the odds ratio. However, the lack evidence does not imply that there was no trial heterogeneity.

The general linear mixed model (GLMM) that allows for trial heterogeneity produced an overall odds ratio estimate of 1.86 (95% CI: 1.24, 2.78). Both the estimate and the

confidence interval were very similar to those from the primary analysis method. The similarity implies that trial heterogeneity was not a major concern. The variance component estimate for the trial heterogeneity effect from the GLLM was 0.13 with a standard error of 0.26. The scale of the component is complex. However, the fact that the estimate was small relative to its standard error again does not provide evidence for trial heterogeneity.

The Mantel-Haenszel odds ratio weights were calculated to examine if there were trials with large influence on the overall odds ratio estimate. On a normalized scale such that the weights add to one, the largest five weights were 0.060, 0.020, 0.019, 0.017, and 0.016. The weight of 0.06 corresponded to the trial divalproex M92822. Except for this trial, no trial accounted for more than one fiftieth of the total weight. The overall odds ratio estimated using the exact method and excluding this trial was 2.12 (95% CI: 1.42, 3.25). This estimate was slightly larger than the estimate with all the trials. However, the two sets of estimates and confidence intervals were qualitatively similar.

6.3.3 Person-Time Analysis

Based on the finding that there was a statistically significant difference in treatment duration between the treatment arms (least-squares means 77 days for placebo versus 73 days for drug), an analysis that adjusts for differences in duration was performed. Figure 5 gives the estimated rate ratio and 95% confidence intervals from this analysis for Suicidal Behavior or Ideation by drug and overall. The overall rate ratio was 1.82 (95% CI: 1.25, 2.68). This result was very similar to the overall odds ratio result, which does not adjusted for difference in treatment duration. Additionally, for each of the 11 drugs, the rate estimate was very similar to the odds ratio estimate.

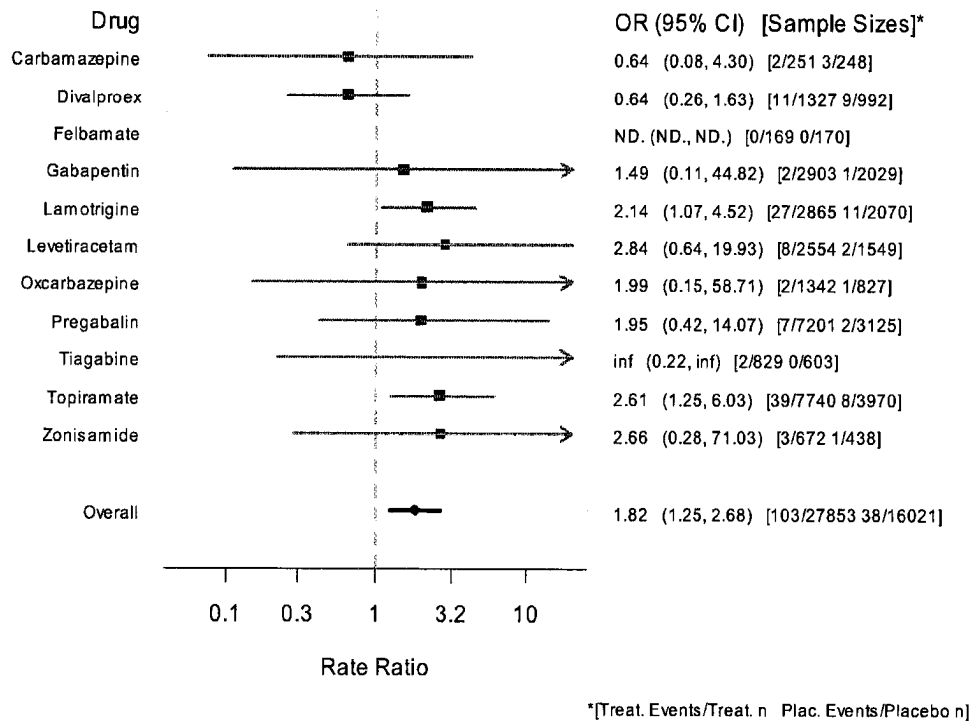


Figure 5: Suicidal Behavior or Ideation Rate Ratio Estimates, Placebo-Controlled Trials.
Note: 18 Patients with missing or zero duration were not included in this analysis.

6.4 Exploratory Analysis

6.4.1 Time-to-Event Analysis

Table 14 shows the number of patients with a Suicidal Behavior or Ideation event and the estimated hazards by disjoint time intervals. The higher hazard of events for the drug-treated patients was observed as early as 1 week from initiating treatment until at least 24 weeks. After 24 weeks, it was not possible to draw conclusions due to the scarcity of data beyond 24 weeks. It appears that the drug effect existed over an extended period and not, for example, just at the initiation of the treatment.

Figure 6 plots Kaplan-Meier incidence curves for the Suicidal Behavior or Ideation events by treatment arm. The spreading of the two curves, at least up to 24 weeks, shows that the higher hazard for the drug patients existed over a period of time.

For the time-to-event analysis as in the other analyses, the first most critical event was used. For all but one patient, this was the first event as well. One patient had a lesser critical event 2 days earlier than the most critical event.

Table 14: Suicidal Behavior or Ideation Hazard Estimates by Treatment Arm, Placebo-Controlled Trials.

Week	Events	Drug		Placebo		
		Patients	Hazard	Events	Patients	Hazard
< 1	10	27337	0.37	5	15780	0.32
1 - 2	13	26077	0.50	4	15192	0.26
2 - 4	27	23979	0.56	11	14029	0.39
4 - 12	34	17591	0.24	14	10312	0.17
12 - 24	12	8139	0.12	3	4592	0.05
≥ 24	7	1862	0.05	1	886	0.02

Notes: Events include only the most critical event for each patient. Patients are “effective sample size” which is the estimated number of patients at the midpoint of interval. Hazard is expressed as events per 1000 patient-weeks. For details see Klein and Moeschberger (2003, p. 152).

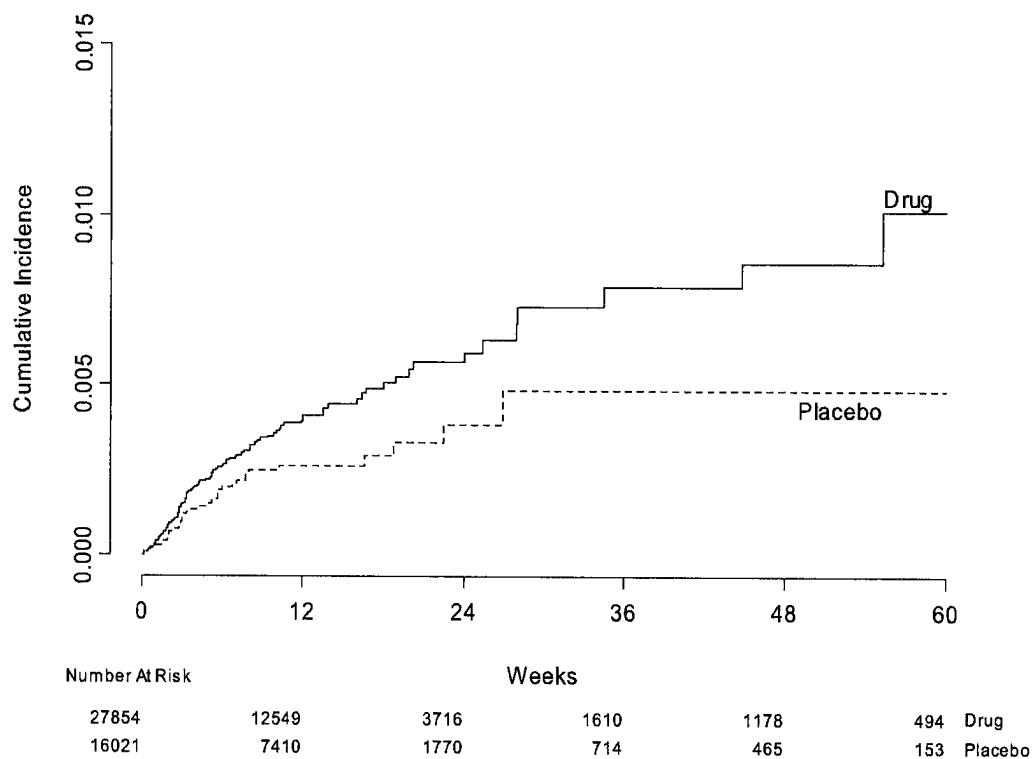


Figure 6: Kaplan-Meier Suicidal Behavior or Ideation Incidence Curves by Treatment Arm, Placebo-Controlled Trials.

6.4.2 Multiple Events

Among the placebo-controlled trials, 9 patients had more than one Suicidal Behavior or Ideation event. Table 15 lists the events for these patients. One patient had two suicide attempts. Another patient had one suicide attempt. The events of the remaining 7 patients were all suicidal ideation.

Table 15: Events from Patients with Multiple Events, Placebo-Controlled Trials.

Patient	Event	Event Day
Carbamazepine 105.301 004004	Ideation	11
	Ideation	12
Divalproex M92822 13709	Ideation	44
	Ideation	234
Divalproex M96493 20101	Ideation	17
	Suicide attempt	19
Lamotrigine P42040 37004	Ideation	5
	Ideation	75
	Ideation	83
	Ideation	88
Lamotrigine SCA3092/0946 63307	Ideation	56
	Ideation	78
Lamotrigine SCAA2010 03168	Suicide attempt	23
	Suicide attempt	30
Topiramate CAPSS168 00013403	Ideation	25
	Ideation	56
Topiramate OBES002 7123	Ideation	51
	Ideation	82
Topiramate PDMD005 10004	Ideation	1
	Ideation	11

7 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

7.1 Drug Groups

Figure 7 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by drug group. The estimated odds ratio for each drug group and its complement were all greater than one. Except for the group made of drugs that are not in the Sodium Channel Blocking group, the confidence intervals for all drug groups did not contain the value of 1. As stated above, the three drug groups are not disjoint. Topiramate is in all three drugs groups, and there were a large number of patients from topiramate trials. Therefore, treatment effects of topiramate can be expected to have large influence on all three drugs classes.

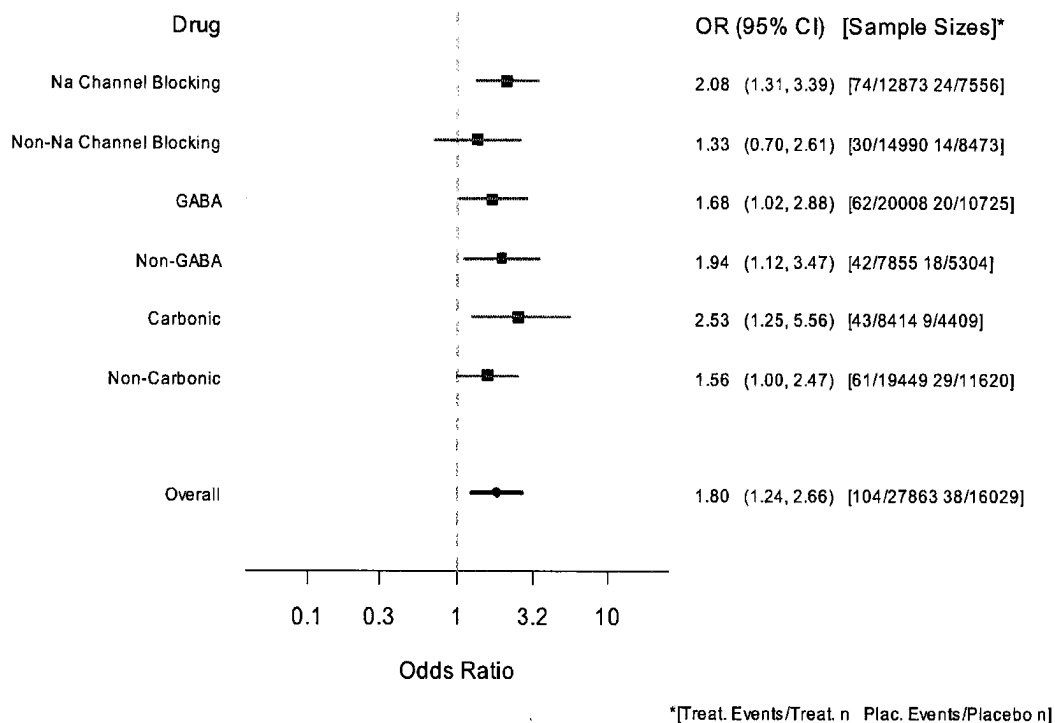


Figure 7: Suicidal Behavior or Ideation Odds Ratio Estimates by Drug Group, Placebo-Controlled Trials.

7.2 Trial Indication

Figure 8 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by indication group. The epilepsy indication group had the highest estimated odds ratio and its confidence interval did not contain the value of 1. The odds ratios for the other two indication groups, psychiatric and other, were greater than 1, but the lower end of the confidence intervals were slightly below 1.

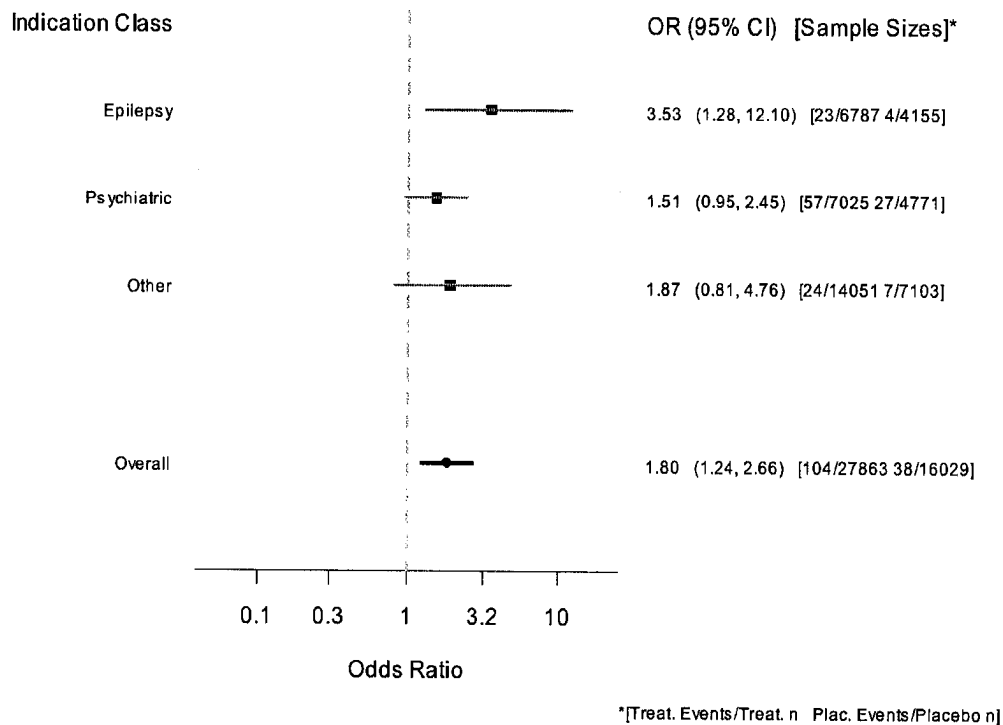


Figure 8: Suicidal Behavior or Ideation Odds Ratio Estimates by Indication Group, Placebo-Controlled Trials.

Although the estimated odds ratio was higher in the epilepsy indication group than in the psychiatric indication group, the excess drug risks in the two indication groups were similar. Table 16 gives estimates of the placebo and drug event rates and the risk difference risk by indication group. The psychiatric indication group had a notably higher placebo event rate than the other indication groups and had the highest risk difference, whereas, the epilepsy indication group had the highest odds ratio.

Table 16: Placebo and Drug Suicidal Behavior or Ideation Event Rates and Risk Difference by Indication, Placebo-Controlled Trials.

Indication	Odds Ratio	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients	Risk Ratio
Epilepsy	3.53	1.0	3.4	2.4	3.5
Psychiatric	1.51	5.7	8.5	2.9	1.5
Other	1.87	1.0	1.8	0.9	1.9
Total	1.80	2.4	4.3	1.9	1.8

Notes: Drug event rate was calculated as the product of the placebo event rate and estimated odds ratio. Risk difference was calculated as the drug event rate minus the placebo event rate. Risk ratio was calculated as the ratio of the drug event rate to the placebo event rate.

7.3 Demographics

7.3.1 Age

Figure 9 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by age group. For all but the 25 – 30 age group, the estimated odds ratios were greater than 1. Only the 31 – 64 age group had a confidence interval that did not contain the value of 1. However, the other age-groups had smaller numbers of patients resulting in wider confidence intervals. Overall, there was no clear pattern across age groups.

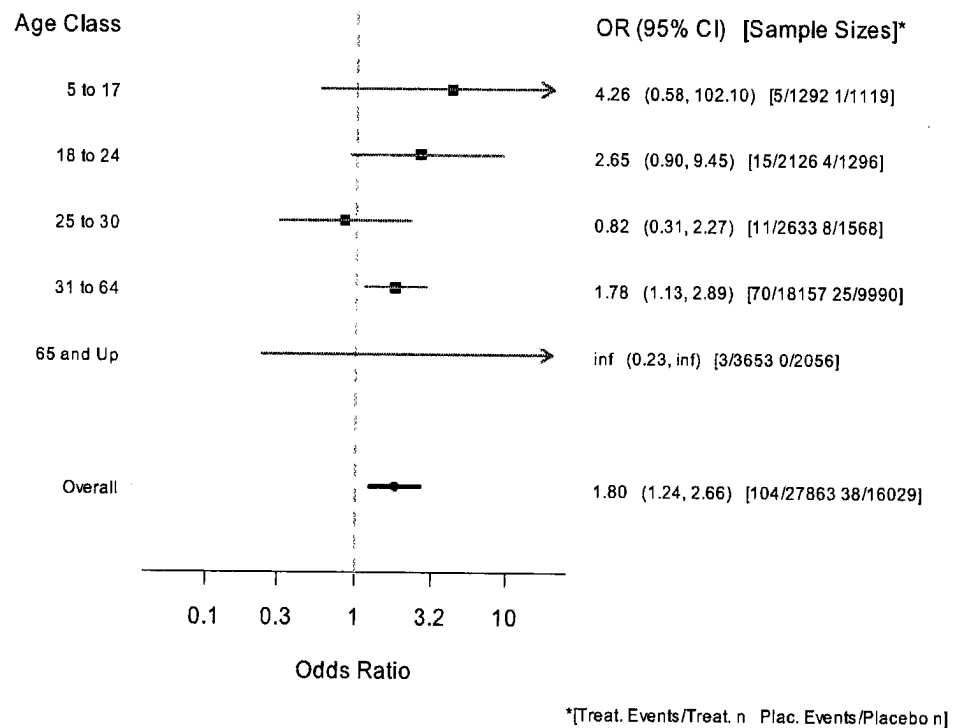


Figure 9: Suicidal Behavior or Ideation Odds Ratio Estimates by Age Group, Placebo-Controlled Trials.

7.3.2 Gender

Figure 10 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation trials by gender. For both females and males, the estimated odds ratios were greater than 1. The confidence interval for males did not contain the value of 1, whereas the confidence interval for females did contain the value of 1.

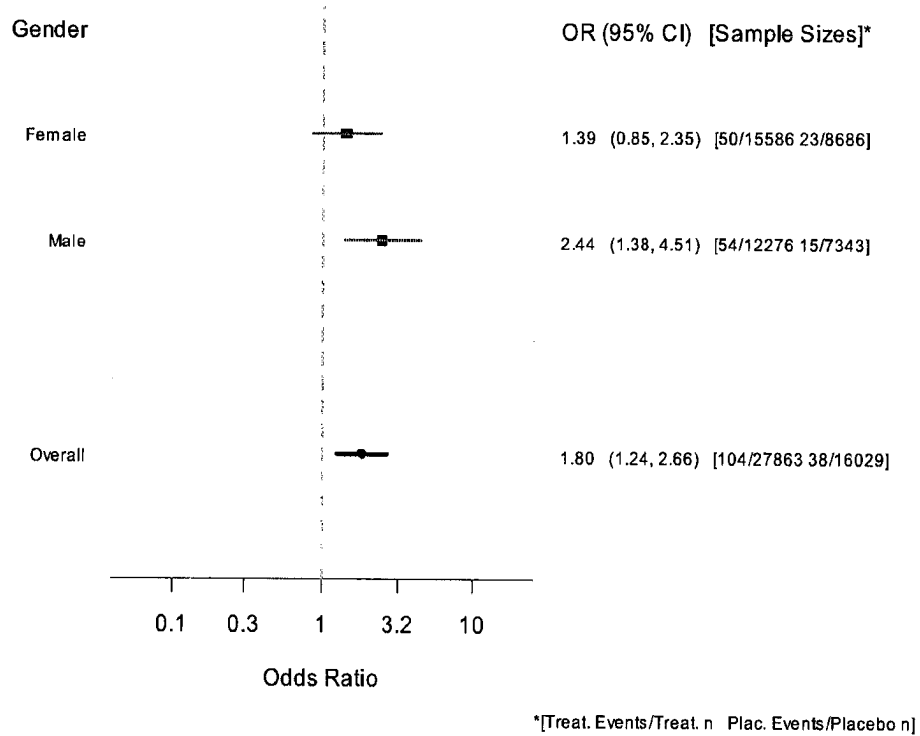


Figure 10: Suicidal Behavior or Ideation Odds Ratio Estimates by Gender, Placebo-Controlled Trials.

7.3.3 Race

Figure 11 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by race. For both the white and other subgroups, the estimated odds ratios were greater than 1. The estimate for the other subgroup was higher than that for white subgroup. The confidence interval for the white subgroup did not contain the value of 1. The confidence interval for other subgroup contained the value of 1, but because of the small number of patients in this group, the confidence interval was wide.

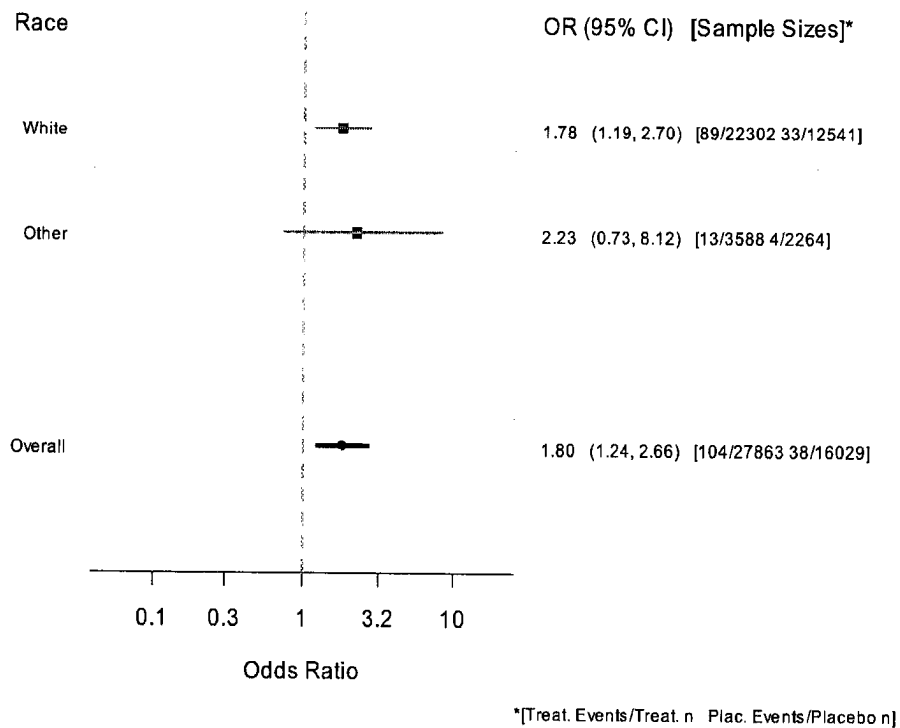


Figure 11: Suicidal Behavior or Ideation Odds Ratio Estimates by Race Group, Placebo-Controlled Trials.

7.3.4 Setting

Figure 12 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by setting. For both settings, the estimated odds ratios were greater than 1. The confidence interval for outpatient setting did not contain the value of 1. The confidence interval for the inpatient or both setting contained the value of 1, but because of the small number of patients in this group, the confidence interval was very wide.

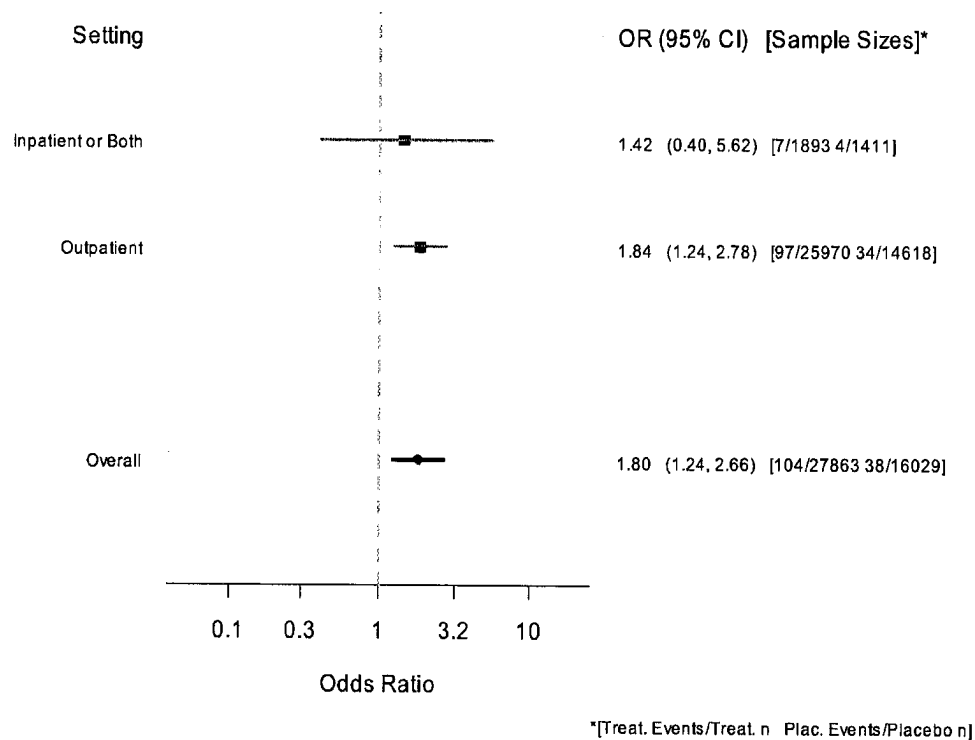


Figure 12: Suicidal Behavior or Ideation Odds Ratio Estimates by Setting, Placebo-Controlled Trials.

7.3.5 Location

Figure 13 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by location. For both North America and Non-North America locations, the estimated odds ratios were greater than 1. However, the estimate for the Non-North America location was notably larger. The confidence interval for Non-North America location did not contain the value of 1. The lower end of the confidence interval for North America location was slightly below the value of 1.

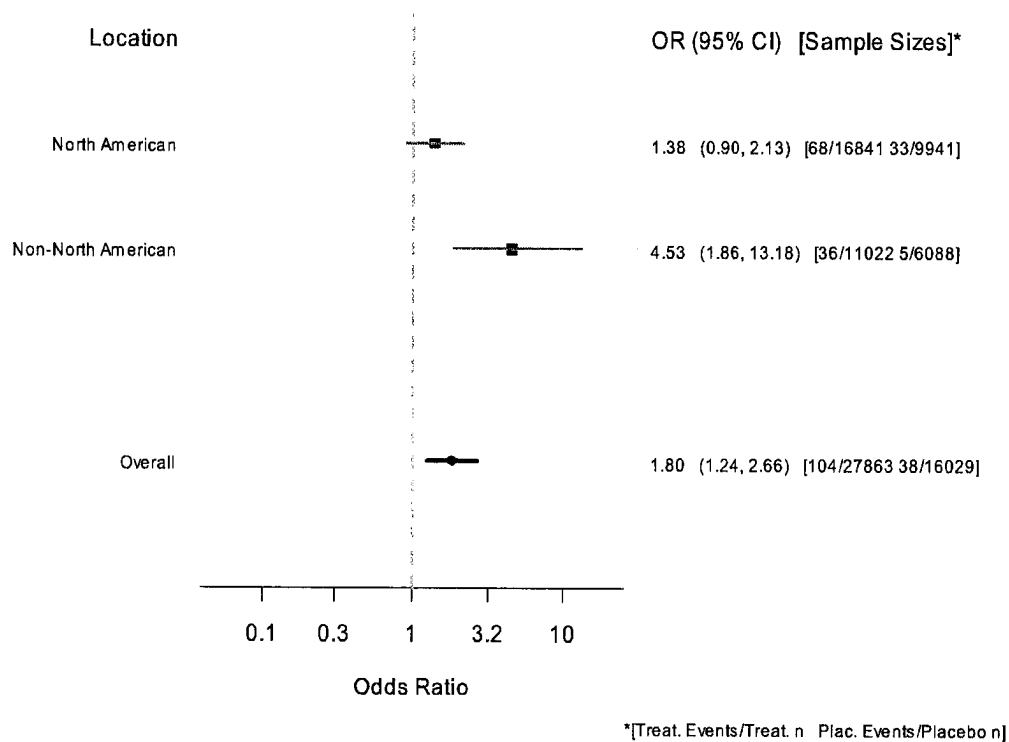


Figure 13: Suicidal Behavior or Ideation Odds Ratio Estimates by Location, Placebo-Controlled Trials.

7.3.6 Comparator Type

Figure 14 gives the estimated overall odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation for placebo-controlled, low-dose-controlled trials, and all trials. The estimated odds ratio was 1.83 (95% CI: 1.26, 2.69) for all controlled trials. This result was very similar to the result for placebo-controlled trial, since most trials were placebo-controlled. The estimated odds ratio for low-dose-controlled trials was 3.09 (95% CI: 0.33, 81.51). The large confidence interval indicates that the result was not precise.

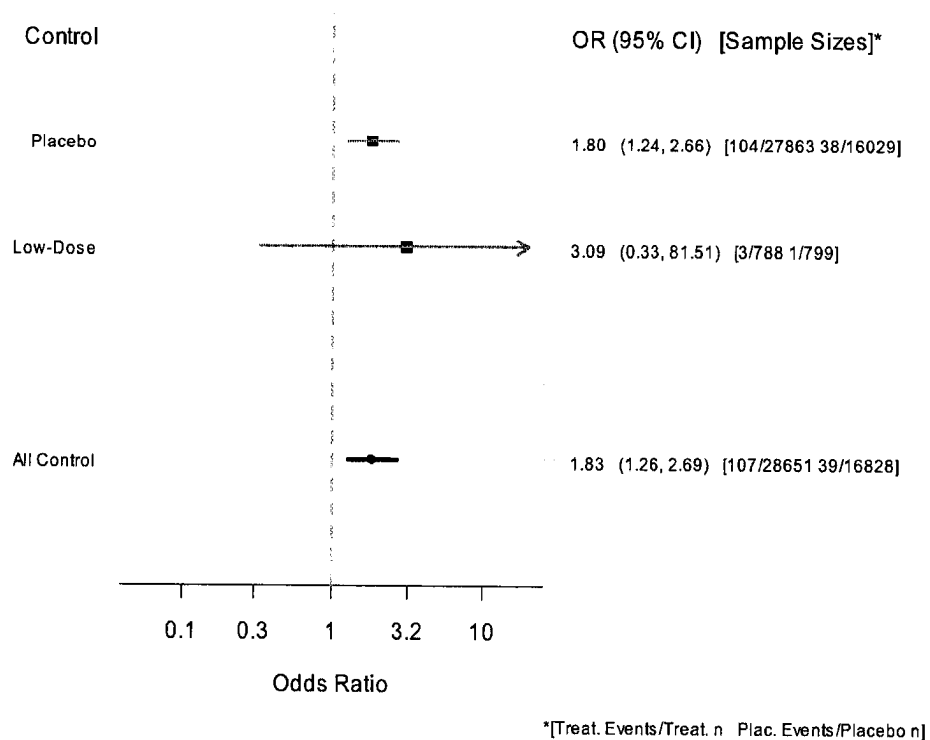


Figure 14: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled and Low-Dose-Controlled Trials.

8 POST-HOC ANALYSES

In addition to the deviations and additions to the SAP noted above, there were analyses performed not specified in the SAP and performed after reviewing the initial analysis.

8.1 Lamotrigine Additional Data

On November 21, 2007, the sponsor of lamotrigine submitted additional data for the drug. The submission included (1) data from three trials that were ongoing at the time of the data requests to the sponsors and (2) 4 additional suicidality events from trials

previously submitted. As stated in Section 3.1.1, in the July 2005 letter to the sponsors, FDA stated that ongoing trials should not be submitted. FDA does not know if there are trials for other drugs that have been completed since July 2005. In the interests of adhering to FDA stated intentions, the additional lamotrigine data was not part of the primary analysis dataset. However, as a sensitivity analysis, the additional data was included.

The three additional lamotrigine trials were placebo-controlled trials and otherwise met the inclusion criteria for the analysis. These trials had a total of 9 Suicidal Behavior or Ideation events. Of these events, 1 was in a drug arm and 8 were in placebo arms.

Among the 4 additional events from trials previously submitted, 3 were in the drug arm and 1 was in the placebo arm.

Figure 15 gives the estimated odds ratio and 95% confidence intervals for Suicidal Behavior or Ideation by drug and overall with the additional lamotrigine data. The estimated overall rate ratio was 1.55 (95% CI: 1.09, 2.21). The estimate was lower than the estimate from the primary analysis, but statistically significant as well.

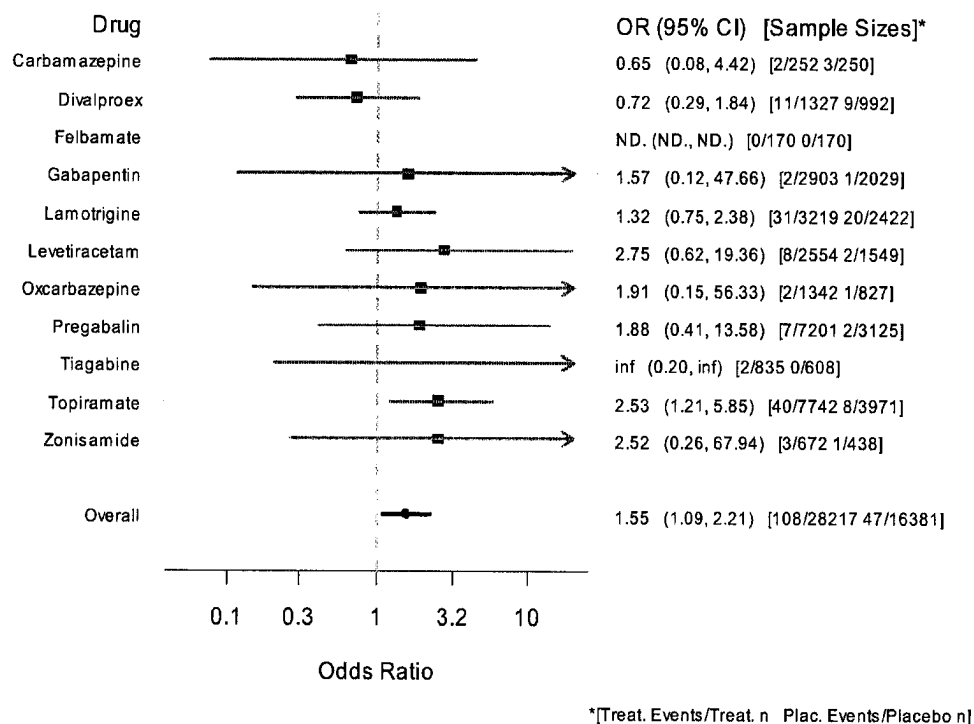


Figure 15: Suicidal Behavior or Ideation Odds Ratio Estimates with Additional Lamotrigine Data, Placebo-Controlled Trials.

8.2 Alternative Age Subgroups

In order to further explore the possibility of an interaction of age with the drug effect, a finer partition of the age subgroups was analyzed post-hoc. The 31 to 64 years age subgroup, which was part of the SAP, was partitioned into 4 age subgroups. Figure 16 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by the post-hoc age groups. As was the case with the prospectively defined age subgroups, there was no clear pattern across age groups.

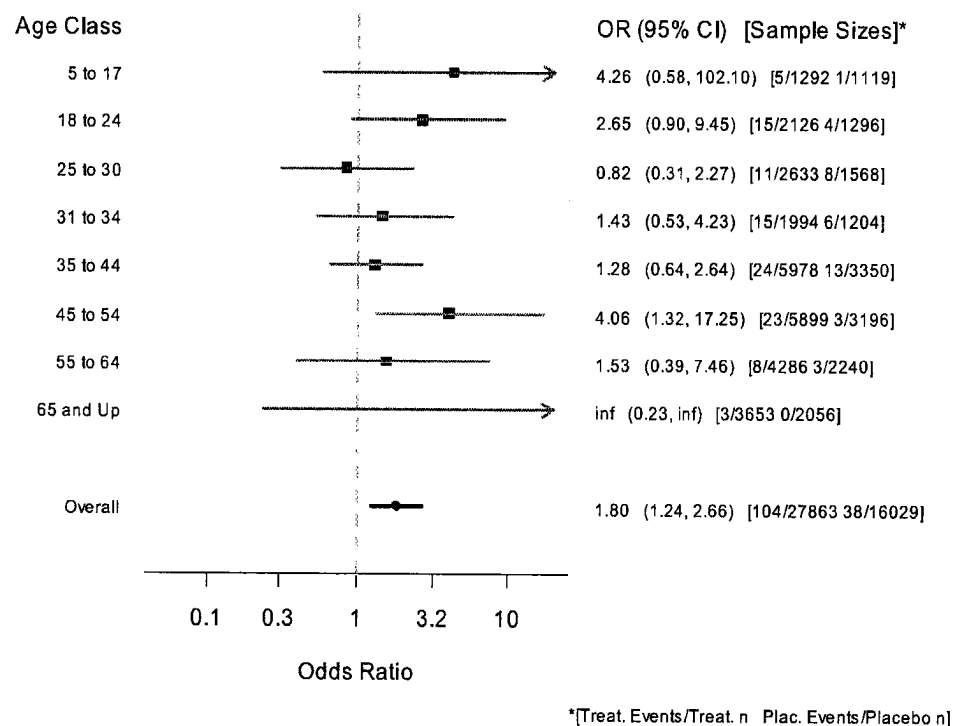


Figure 16: Suicidal Behavior or Ideation Odds Ratio Estimates by Post-Hoc Age Group, Placebo-Controlled Trials.

9 SUMMARY AND CONCLUSIONS

9.1 Review Summary

This reviewed analyzed data from 210 placebo-controlled and low-dose-controlled trials of antiepileptic drugs. The trials came from 11 different antiepileptic drugs. The indications for the trials included epilepsy, psychiatric disorders, and other indications. The primary focus of the review was on the 199 placebo-controlled trials. In these trials,

there were 27,863 patients in the drug arms and 16,029 patients in the placebo arms that met the analysis criteria of being at least 5 years of age.

There were no statistical differences among the baseline characteristics of the drug and placebo patients for age, gender, race, and location. The placebo patients had a statistically lower treatment discontinuation rate than the drug patients. Likewise, the placebo patients had statistically higher treatment duration (77 days for placebo versus 73 days for drug).

There were 4 completed suicides among drug patients and none among placebo patients. The majority of suicidality events for both drug and placebo patients were Suicidal Ideation. The second most frequent type of event was Suicide Attempt. Without adjusting for differences among trials, 0.37% of the drug patients had a Suicidal Behavior or Ideation event versus 0.24% of the placebo patients.

A meta-analysis was conducted to estimate an overall treatment effect for drug versus placebo patients and for various subgroups. The meta-analysis controlled for differences in background rates of events among the trials.

Overall, the drugs were associated with statistically significant increased the risk of Suicidal Behavior or Ideation relative to placebo. The estimated overall odds ratio was 1.80 (95% CI: 1.24, 2.66). There was consistency among the results for individual drugs. The estimated odds ratio was greater than 1 for 8 drugs and less than 1 for 2 drugs. The estimated odds ratio was greater for the Suicidal Behavior endpoint than the Suicidal Ideation endpoint.

Several sensitivity analyses were performed to examine the robustness of the result to the sparseness of the events, heterogeneity of the treatment effect, and differences in treatment duration between the placebo and drug arms. All the sensitivity analyses produced very similar results to the results of primary analysis for both the overall odds ratio and the individual drug odds ratios.

The higher risk of events for the drug-treated patients was observed as early as 1 week from initiating treatment until at least 24 weeks. After 24 weeks, it was not possible to draw conclusions due to the scarcity of data beyond 24 weeks.

Several subgroups were considered. Indication and location appeared to have the largest effects among the subgroups considered. The epilepsy indication subgroup had the largest estimated odds ratio compared to the psychiatric indication subgroup and the other indication subgroup. However, the psychiatric indication subgroup had the largest placebo risk of events. The result does not appear to be driven by particular drugs, since several drugs contributed comparable numbers of patients to the epilepsy subgroup. The estimated odds ratio for the Non-North American subgroup was notably larger than that of North American subgroup.

There was no obvious pattern in the risk with the age subgroups. For 4 of the 5 age subgroups, the estimated odds ratios were greater than 1. Likewise, there were no patterns in the risks for subgroups based on gender, race, setting, and prespecified drug groups.

9.2 Conclusions

In conclusion, antiepileptic drugs are associated with increased risk of suicidality relative to placebo in randomized placebo-controlled trials. The effect appears consistent among the group of 11 drugs. There are 1.9 per 1000 (95% CI: 0.6, 3.9) more antiepileptic drug patients than placebo patients who experience Suicidal Behavior or Ideation. In terms of adjusted risk estimates for the treatment groups, 0.43% of the drug patients experience Suicidal Behavior or Ideation compared to 0.24% of the placebo patients.

There is no obvious subgroup of patients to which the increased risk is specifically attributed. The increased risk was seen in almost all subgroups, although epileptic and Non-North American patients may have higher relative risks.

10 REFERENCES

- Cytel 2005. StatXact 7 PROCs for SAS Users. Cambridge (MA): Cytel Inc.
- Greenland S, Robins JM 1985. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 41:55-68
- Klein JP, Moeschberger ML 2003. *Survival Analysis* 2nd Ed. New York (NY):Springer.
- McCulloch CE, Searle SR 2001. *Generalized, Linear, and Mixed Models*. New York (NY): John Wiley & Sons.
- Posner K, Oquendo MA, Gould M, Stanley B, Davies M 2007. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 164:1035-43.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mark Levenson

5/23/2008 12:10:57 PM

BIOMETRICS

This version replaces the March 5, 2008 version.

George Rochester

5/23/2008 03:58:10 PM

BIOMETRICS

This document is a revised review which reflects the
most recent updates to the database.